

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Appellant(s): Dirk Beher, et al.
Application Number: 10/566,844
Filing Date: February 1, 2006
Title of the Invention: Treatment of Alzheimer's Disease and Related
Conditions
Examiner: Savitha M Rao
Art Unit: 1614

APPEAL BRIEF

STATEMENT OF THE REAL PARTY IN INTEREST

The real party in interest is Merck Sharp & Dohme Limited, a wholly owned
5 subsidiary of Merck & Co., Inc.

STATEMENT OF RELATED CASES

None.

10 JURISDICTIONAL STATEMENT

The Board has jurisdiction under 35 U.S.C. 134(a). The examiner mailed a
final rejection on April 29, 2009, setting a three-month shortened statutory period
for response. The shortened statutory period for replying to the final rejection
15 expired on July 29, 2009. A notice of appeal was filed on July 29, 2009. The time
for filing an appeal brief is two months after the filing of a notice of appeal. Rule
41.37(c). The appeal brief is being filed on September 29, 2009.

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TABLE OF AUTHORITIES

<u>Takeda Chemical Industries v. Mylan Laboratories</u> , 492 F.3d 1350 (Fed.Cir.2007).....	7
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STATUS OF AMENDMENTS

- 5 An Amendment after Final Rejection filed June 10, 2009, was entered by the
examiner.

GROUND OF REJECTION TO BE REVIEWED

- Rejection of Claim 7 as obvious over Ford-Hutchinson (EP 0 307 077) as
evidenced by Patani (Patani et al., Chemical Reviews, 1996, vol. 96 (8), pages
10 3147-3176) in view of Watanbe (US 6,514,984).

STATEMENT OF FACTS

- Fact 1. Ford-Hutchinson described a genus of tetrahydrocarbazole-1-
alkanoic acids (page 4, lines 15 to page 5, line 29 and claim 1). Fact 2. Ford-
Hutchinson additionally discloses the compound 9-*p*-chlorobenzyl-6-isopropyl-
15 1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid (page 8, line 10-30, page 10, lines 1 and
11 and page 37, lines 25-40). Fact 3. Ford-Hutchinson describes the compounds
therein as useful for improving cyclosporine therapy (page 2, line 4).

- Fact 4. Patani describes the structure activity relationship of 1-[(2-
hydroxyethoxy)methyl]-5-benzyluracils for inhibition of liver uridine
20 phosphorylase (UrdPase) and demonstrates that substitution of CF₃ for Cl at the 3-

position resulted in less potent analogues (page 3172, column 1, first paragraph).

Fact 5. Patani describes the structure activity relationship of 3-

(benzoylamino)benzodiazepines for antagonist activity at the chlolescystokinin-A

(CCK-A) receptor and demonstrates that substitution of CF₃ for Cl at the 4-position

5 of the benzoyl group resulted in retention of CCK-A activity (page 3172, column 1, second paragraph).

Fact 6. Watanbe describes a method for the prevention and treatment of Alzheimer's disease by administering to a human in need thereof an effective amount of a substituted tricyclic secretory phospholipase A2 (sPLA₂) inhibitor

10 (abstract). Fact 7. Watanbe describes a genus of carbazole compounds. (col. 10, lines 11-65). Fact 8. Watanbe describes suitable formulations being those comprising a therapeutically effective amount of sPLA₂ inhibitor together with a pharmaceutically diluent or carrier, the composition being adapted for the particular route of administration. (col. 55, lines 49-57).

15

ARGUMENT

ERRORS IN REJECTION BASED ON FORD-HUTCHINSON AS EVIDENCED BY PATANI IN VIEW OF WATANBE

20

CLAIM 7

The examiner argues that one skilled in the medicinal chemistry art with knowledge of Ford-Hutchinson would have been motivated to modify compound

24 described therein to synthesize those presently claimed. Final Rejection mailed April 29, 2009, page 6, lines 1-8. In response, appellants previously pointed out to the examiner why the examiner is believed to have erred. Reply to Non-Final Office Action dated February 9, 2009, pages 1 to 3 and Amendment After Final

5 Rejection dated June 10, 2009, page 4. The response is, first, the fact that a claimed subgenus is encompassed by a prior art genus is insufficient by itself to establish a *prima facie* case of obviousness. One skilled in the art must be motivated to select the claimed sub-genus from the disclosed prior art genus. Here, there are a number of possible substitutions taught by the genus of Ford-
10 Hutchinson and there is no motivation for one skilled in the art to modify Ex. 24 of Ford-Hutchinson by substituting CF₃ at the 4-position of the benzyl portion of Formula III and a hydrocarbon of 2 to 10 carbon atoms on the benzylic carbon.

Second, none of the actual examples disclosed in Ford-Hutchinson have a hydrocarbon of 2 to 10 carbon atoms on the benzylic carbon, thus teaching away
15 from the present invention. Appellants wish to point out an error in the arguments contained in the Reply to Non-Final Office Action dated February 9, 2009 at page 2, first paragraph. Compound 66 of Ford-Hutchinson contains a CF₃ group at the 4 position of the benzyl group.

Furthermore, appellants present a new argument that was not previously
20 presented to the examiner. The new argument is that one skilled in the art would

not have selected Example 24 from Ford-Hutchinson as a lead compound from which to make further modifications to seek improved properties. Takeda Chemical Industries v. Mylan Laboratories, 492 F.3d 1350, 1357 (Fed.Cir.2007).

In Ford-Hutchinson, test results are described for compounds 1, 37, 50 and 63, not
5 24.

The Examiner also argues that one of ordinary skill in the art would have been motivated to try out the range of substituents taught by Ford-Hutchinson to arrive at the instantly claimed compounds. Final Rejection mailed April 29, 2009, page 8, lines 8-10. The Examiner further argues that the instantly claimed
10 compounds are explicitly suggested by Ford-Hutchinson within a finite list of compounds encompassed by the generic compounds and the exemplified compounds and as such renders the instantly claimed compounds and compositions obvious. Final Rejection mailed April 29, 2009, page 10, lines 13-16. In response, Appellants previously pointed out to the examiner why the examiner is believed to
15 have erred. Reply to Non-Final Office Action dated February 9, 2009, page 3.

The response is that obvious to try is not the proper standard to conduct an obviousness determination for chemical compounds. "In cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish a
20 prima facie case of obviousness." Takeda, 492 F.3d at 1357.

The examiner further argues that Patani teaches that Cl and CF₃ are bioisosteres and one can be substituted for the other. Final Rejection mailed April 29, 2009, page 6, lines 9-11. In response, Appellants previously pointed out to the examiner why the examiner is believed to have erred. Reply to Non-Final Office
5 Action dated February 9, 2009, pages 2 to 3. The response is that Patani teaches substitution on entirely different core molecules for different biologic targets and would in no way be utilized by the ordinarily skilled artisan in designing compounds that limit cyclosporine induced nephrotoxicity or modulate the action of gamma secretase. Furthermore, Patani itself demonstrates the unpredictability
10 of the chemical arts as substitution of CF₃ for Cl resulted in less potent analogues for the demonstrated UrdPase inhibitors but retention of activity for the CCK-A receptor antagonists.

The Examiner further argues Watanbe provides additional motivation as structurally similar compounds and compositions have been shown to be used
15 for the treatment of Alzheimer's disease. Final Rejection mailed April 29, 2009, page 8, lines 11-12. In response, Appellants previously pointed out to the examiner why the examiner is believed to have erred. Reply to Non-Final Office Action dated February 9, 2009, page 3. The response is that the instant claims require a C(R²)₂CO₂H group at a fixed position on the cyclohexene ring adjacent to
20 the indole nitrogen. The nearest Watanbe comes to this is an amide or hydrazide

group, attached directly to the ring (no $-C(R^2)-$ spacer) at the opposite end, i.e., pointing in entirely the wrong direction. Thus, Watanbe would in no way motivate the ordinarily skilled chemist to modify the compounds of Ford-Hutchinson to arrive at the compounds presently claimed.

5 Appellants wish to point out an error in the arguments contained in the Reply to Non-Final Office Action dated February 9, 2009 at page 3, second paragraph. The argument states that Watanbe does not specifically teach CF_3 substitution on the phenyl ring. However, Watanbe does not specifically teach 4- CF_3 substitution on the phenyl ring or substitution with 2 to 10 carbon atoms on the
10 benzylic carbon.

 Furthermore, appellants present a new argument that was not previously presented to the examiner. The new argument is that one skilled in the art would in no way combine the teachings of Ford-Hutchinson (improving cyclosporine therapy) with Watanbe (Alzheimer's disease) as the compounds disclosed therein
15 are directed to unrelated utilities.

CONCLUSION

Appellants request that the Board of Patent Appeals and Interferences reverse the outstanding rejections of claim 7.

Please charge deposit account 13-2755 for fees due in connection with this appeal brief. If any time extensions are needed for the timely filing of the present appeal brief, appellants petition for such extensions and authorize the charging of deposit account 13-2755 for the appropriate fees.

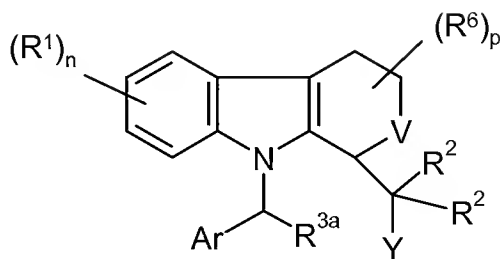
Respectfully submitted,

By /Raynard Yuro, Reg. # 45570/
Raynard Yuro
Reg. No. 45,570
Attorney for Appellants

Merck & Co., Inc.
RY60-30
P.O. Box 2000
Rahway, NJ 07065-0907
Phone: (732) 594-0182
Fax: (732)594-4720
email:
raynard_yuro@merck.com

CLAIMS APPENDIX

Claim 7 (Rejected) A compound having formula III:



III

or a pharmaceutically acceptable salt thereof, wherein

V represents a bond, CH_2 or CH_2CH_2 ;

n is 0, 1, 2 or 3;

each R^1 is independently selected from nonaromatic hydrocarbon groups of up to 6 carbon atoms and $(CH_2)_q-W$ where q is 0, 1 or 2 and W represents halogen, CN, CF_3 , OR^4 , $N(R^4)_2$, SR^4 , CO_2R^4 , tetrazole, $CON(R^4)_2$, $SO_2N(R^4)_2$, COR^5 , $OCOR^5$ or phenyl or heteroaryl either of which optionally bears up to 3 substituents selected from halogen, CF_3 , OCF_3 , CN, OH, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio or C_{1-4} alkoxycarbonyl;

R^{3a} represents a hydrocarbon group containing from 2 to 10 carbon atoms which is optionally substituted with halogen, CF_3 , C_{1-4} alkoxy or C_{1-4} alkylthio;

R^4 represents H or a hydrocarbon group of up to 7 carbon atoms, optionally substituted with halogen, CN, CF_3 , OH, C_{1-4} alkoxy or C_{1-4} alkoxycarbonyl; or two R^4 groups attached to the same nitrogen atom may complete a 5- or 6-membered heterocyclic ring;

5 R^5 represents R^4 that is other than H;

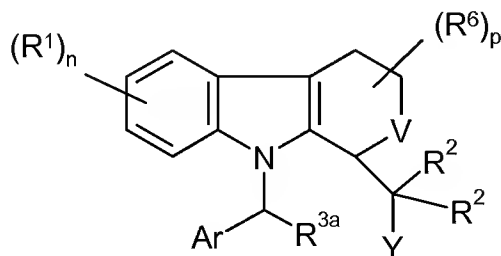
R^6 represents C_{1-6} alkyl, C_{2-6} alkenyl or phenyl, benzyl or heteroaryl, said phenyl, benzyl or heteroaryl optionally bearing up to 3 substituents selected from halogen, CN, CF_3 , OCF_3 , OR^4 , CO_2R^4 , COR^5 , $OCOR^5$ and C_{1-4} alkyl;

p is 0, 1 or 2; and

10 Y represents CO_2H , Ar represents 4-trifluoromethylphenyl, and both R^2 groups represent H.

CLAIM SUPPORT AND DRAWING ANALYSIS APPENDIX

Claim 7 A compound having formula III:



{Page 14, line 25; original claim 7}

5

III

or a pharmaceutically acceptable salt thereof, {Page 15, lines 3-4; original claim 7}

wherein

V represents a bond, CH₂ or CH₂CH₂; {Page 15, lines 1 to 2; Page 3, line

10 12; original claim 7}

n is 0, 1, 2 or 3; {Page 15, lines 1 to 2; Page 3, line 22; original claim 7}

each R¹ is independently selected from nonaromatic hydrocarbon groups of up to 6 carbon atoms and (CH₂)_q-W where q is 0, 1 or 2 and W represents halogen, CN, CF₃, OR⁴, N(R⁴)₂, SR⁴, CO₂R⁴, tetrazole, CON(R⁴)₂, SO₂N(R⁴)₂, COR⁵,

15 OCOR⁵ or phenyl or heteroaryl either of which optionally bears up to 3

substituents selected from halogen, CF₃, OCF₃, CN, OH, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋

₄alkylthio or C₁₋₄alkoxycarbonyl; {Page 15, lines 1 to 2; Page 3, line 23 to page 4, line 2; original claim 7}

R^{3a} represents a hydrocarbon group containing from 2 to 10 carbon atoms which is optionally substituted with halogen, CF₃, C₁₋₄alkoxy or C₁₋₄alkylthio;

5 {Page 14, lines 27 to 28; original claim 7}

R⁴ represents H or a hydrocarbon group of up to 7 carbon atoms, optionally substituted with halogen, CN, CF₃, OH, C₁₋₄alkoxy or C₁₋₄alkoxycarbonyl; or two R⁴ groups attached to the same nitrogen atom may complete a 5- or 6-membered heterocyclic ring; {Page 4, line 6 to 9; original claim 7}

10 R⁵ represents R⁴ that is other than H; {page 4, line 10; original claim 7}

R⁶ represents C₁₋₆alkyl, C₂₋₆alkenyl or phenyl, benzyl or heteroaryl, said phenyl, benzyl or heteroaryl optionally bearing up to 3 substituents selected from halogen, CN, CF₃, OCF₃, OR⁴, CO₂R⁴, COR⁵, OCOR⁵ and C₁₋₄alkyl; { Page 15, lines 1 to 2; Page 4, lines 12-14; original claim 7}

15 p is 0, 1 or 2; { Page 15, lines 1 to 2; Page 4, line 11; original claim 7} and

Y represents CO₂H, Ar represents 4-trifluoromethylphenyl, and both R² groups represent H. {Page 15, lines 8-10; original claim 7}

MEANS OR STEP PLUS FUNCTION ANALYSIS APPENDIX

None.

EVIDENCE APPENDIX

None.

5 RELATED CASES APPENDIX

None.